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- (71) Applicant (*for all designated States except US*): **PANTARHEI BIOSCIENCE B.V.** [NL/NL]; P.O. Box 464, NL-3700 AL Zeist (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **VERHAAR, Mark**, Theodoor [NL/NL]; Mudaheerd 60, NL-9737 XB Groningen (NL). **KOCH, Thomas** [DE/NL]; Jozef Israelsstraat 12 A, NL-9718 GJ Groningen (NL). **WARMERDAN, Erwin**, Gerardus, Jacobus [NL/NL]; Neerstraat 6, NL-6004 KB Weert (NL).
- (74) Agents: **VAN WESTENBRUGGE, Andries et al.**; Nederlandsch Octrooibureau, Scheveningseweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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(54) Title: SYNTHESIS OF ESTETROL VIA ESTRONE DERIVED STEROIDS

(57) Abstract: A process is provided for the making of estetrol starting from a 3-A-oxy-estra 1,3,5(10),15-tetraen-17-one, wherein A is an C₁-C₅ alkyl group, preferably a methyl group, or a C₇ - C₁₂ benzylic group, preferably a benzyl group. This process is particularly suitable to industry.

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(84) Designated States (*regional*): ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

PCT/NL 03/00782

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>FISHMAN J ET AL: "SYNTHESIS OF EPIMERIC 15-HYDROXYESTRIOLS, NEW AND POTENTIAL METABOLITES OF ESTRADIOL"</p> <p>JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 33, no. 8, August 1968 (1968-08), pages 3133-3135, XP009004834</p> <p>ISSN: 0022-3263</p> <p>cited in the application</p> <p>the whole document</p> <p>-----</p> <p>-/-</p>	1-17,22, 23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 January 2004

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seelmann, I

INTERNATIONAL SEARCH REPORT

PCT/NL 03/00782

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAMBARA T ET AL: "SYNTHESIS OF ESTEROL MONOGLUCURONIDES" STERIODS, BUTTERWORTH-HEINEMANN, STONEHAM, MA, US, vol. 27, no. 1, January 1976 (1976-01), pages 111-122, XP009004815 ISSN: 0039-128X cited in the application compounds I-VIA	1-17, 22, 23
X	SUZUKI E ET AL: "Synthesis of 15alpha-hydroxyestrogen 15-N-acetylglucosaminides" STERIODS: STRUCTURE, FUNCTION, AND REGULATION, ELSEVIER SCIENCE PUBLISHERS, NEW YORK, NY, US, vol. 60, no. 3, 1 March 1995 (1995-03-01), pages 277-284, XP004026551 ISSN: 0039-128X cited in the application compound 1A-3B	1-17, 22, 23
X	POIRIER D ET AL: "SYNTHESIS OF 17BETA-ESTRADIOL DERIVATIVES WITH N-BUTYL, N-METHYL ALKYLAMIDE SIDE CHAIN AT POSITION 15" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 47, no. 37, 1991, pages 7751-7766, XP001122350 ISSN: 0040-4020 compounds 8 and 9	18-21
X	DE 21 29 943 A (MERCK & CO INC) 23 December 1971 (1971-12-23) example 10	31
X	EP 0 646 592 A (KUREHA CHEMICAL IND CO LTD) 5 April 1995 (1995-04-05) examples 1,2	28,29
X	US 3 433 785 A (PHILLIPS DONALD K ET AL) 18 March 1969 (1969-03-18) example 1	24,25
X	DD 144 266 A (KASCH HELMUT; PONSOLD KURT) 8 October 1980 (1980-10-08) example 1	30,31
X	US 3 138 588 A (HERCHEL SMITH) 23 June 1964 (1964-06-23) examples 3,6,12	29
X	US 3 177 206 A (SMITH LELAND L ET AL) 6 April 1965 (1965-04-06) example 1	29,30

INTERNATIONAL SEARCH REPORT

PCT/NL 03/00782

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet) -----

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-17, 22, 23, 26, 27

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17,22,23,26,27

A process for the preparation of (1) and compounds according
to formula 2 and 3

2. claims: 18-21

A process for the preparation of (6)

3. claim: 24

A compound according to formula 5

4. claim: 25

A compound according to formula 4

5. claim: 28

A compound according to formula 8

6. claim: 29

A compound according to formula 9

7. claim: 30

A compound according to formula 10

8. claim: 31

A compound according to formula 11

INTERNATIONAL SEARCH REPORT

PCT/NL 03/00782

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